Emerging clinical applications of photoacoustic imaging.

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Editorial

Photoacoustic (PA) or optoacoustic imaging is a relatively new imaging modality based on the detection of light-excited ultrasound waves, has emerged as one of the most exciting research areas in biomedical imaging over the past decade [1-4]. In PA imaging, nanosecond pulsed (or modulated) electromagnetic radiation is delivered into tissues to excite ultrasound waves *via* photon absorption and thermos-elastic expansion. Subsequently ultrasound detection and image reconstruction are performed to generate an image of tissue optical absorption. This hybrid imaging technique thus combines advantages from both optical and ultrasound imaging, by encoding discriminative optical absorption contrast into ultrasound waves. Furthermore, PA imaging is capable of scaling its spatial resolution and imaging depth, enabling imaging of subjects ranging from organelles, cells, tissues, to organs, and with spatial resolution ranging from sub-micrometres to sub-millimetres. As such, PA imaging holds tremendous potential for a wide range of clinical applications.

PA Imaging of the Breast

Breast imaging has been an original research focus of PA imaging since 1990s [5-6]. This research interest has been driven by fact that current imaging modalities for breast cancer screening and diagnosis have limitations. X-ray imaging is the gold standard for breast cancer screening, as it can provide high spatial resolution 2D images of the breast. However, X-ray mammography, performed with ionizing radiation and painful breast compression, is not sensitive in dense breasts [7]. Diagnosis is based on the results obtained from X-ray mammography, ultrasonography and biopsy. MRI is sometimes used when there is lack of consistent results obtained from X-ray mammography and ultrasonography. However, ultrasonography suffers from limited soft tissue contrast, inherent speckle noise, and strong operator dependence. PA imaging hold great potential to address many of these limitations by providing non-invasive, high resolution images of increased vascular density that is associated with breast malignancies [8-9].

The application of PA (or thermoacoustic) imaging for breast cancer detection was first introduced by Oraevsky et al. [10] and Kruger et al. [11] in 2001. In 2007, Manohar et al. reported the first results on 3D imaging of breast cancer in human subjects [12] with a system they called the Twente Photoacoustic Mammoscope (PAM), which produces 3D images in regions of interest. In this work, in four of the five cases of malignancies studied, PAM was able to visualise regions with higher PA amplitude than the normal background tissue. A clinical study on 11 patients reported in 2011 from the same group [13] has shown that PA image contrasts for breast malignancies are independent of radiological breast density, which makes PA imaging more reliable for young patient compared to X-ray mammography. In 2015, they reported their recent clinical data on 14 patients [14]. In which, malignant lesions visualised in PA images were found to possess three types of appearances, which were consistent with the contrast enhancement types generally reported in MRI of breast malignancies. Recently M. Toi, et al. reported their findings from a study on 22 malignant cases with a PA imaging system that employed a hemispherical-shaped detector array [15]. It was found that PA images were able to visualise morphologically abnormal peritumoral blood vessel features and tumour hypoxia.

Clinical cases studies on breast cancer imaging reported so far have been very promising. However, imaging at large depths required in this application represents a major challenge due to the rapid reduction of PA signal amplitude with increasing imaging depth. This requires advanced piezoelectric transducers that are optimised for breast imaging [16-18], or novel ultrasound sensing mechanisms such as optical ultrasound detection [19].

Interventional PA Imaging

Precise and efficient device guidance lies at the heart for minimally invasive procedures for identifying procedural targets and thus avoiding potential complications. A wide range of minimally invasive procedures are performed under ultrasound image guidance, including breast biopsy, nerve blocks, foetal interventions, and prostate brachytherapy therapy. However, due to limited soft tissue contrast and specificity, ultrasound imaging cannot reliably identify tissue targets in many clinical contexts. A clinical ultrasound array based PA imaging system could potentially address this limitation by providing both structural information from conventional ultrasound imaging and spectroscopic optical contrast from PA imaging [20]. However, conventional surface-illumination based non-invasive PA imaging systems suffer from limited imaging depths associated with the rapid reduction of PA signal amplitude due to light attenuation in soft tissues. Interventional PA imaging addresses this problem by delivering the excitation light inside the body *via* an optical fibre that is positioned within the working channel of an interventional device, and detecting ultrasound with a clinical ultrasound array.

Interventional PA imaging has attracted increasing research interests over the past few years. Piras developed an interventional PA imaging system for breast biopsy guidance, with light delivery *via* an optical fibre embedded in the biopsy needle [21]. The group of Desjardins developed interventional

PA imaging systems for guidance of nerve blocks and foetal interventions [20-23]. In which, excitation light with multiple wavelengths were delivered inside tissue through a multimode optical fibre to identify critical structures such as blood vessels and nerves during the procedures. Further to facilitate visualisation of the needle tip with ultrasound imaging to avoid damaging critical tissue structures, they developed an active method called ultrasonic tracking [23-27]. In which a fibre optic ultrasound sensor was integrated into the needle cannula to receive ultrasound transmissions from the external ultrasound array. These ultrasound transmissions were then processed to form an unambiguous image of the tip of the interventional device. Bell et al. reported an interventional PA system for visualisation of prostate brachytherapy seeds during prostate brachytherapy therapy [28]. Recently, Singh et al. proposed a method, called photoacoustic-guided focused ultrasound (Perfusion), to remove reflection artefacts caused by the high PA signals reflecting off the prostate brachytherapy seeds [29].

Interventional PA imaging could be valuable for real-time guidance of minimally invasive procedures, by providing molecular contrast and structure information in a hybrid imaging modality. It could pave the way for clinical translations of PA imaging by addressing the limited imaging depths issues associated with conventional non-invasive PA imaging systems.

Intravascular PA Imaging

The sudden rupture of a carotid atherosclerotic plaque remains one of the main causes of stroke and stroke-induced death. Lipid-laden macrophages are known to play an important role in the formation of atheroma [30]. Duplex ultrasound imaging is widely used to estimate the degree of carotid artery stenosis, but this modality does not provide enough sensitivity and specificity in detecting the plaque morphology. Multispectral PA imaging promises to supplement ultrasound imaging by providing spatially resolved tissue compositions of the plaque such as lipid and haemoglobin content.

The most common approach for an intravascular PA imaging system is the integration of a light delivery fibre into an intravascular ultrasound imaging system [31-32]. Typically, excitation light with two ranges of wavelengths (centred at wavelengths in the vicinity of 800 nm and 1200 nm) are used to provide spectroscopic specificity in detecting intraplaque haemorrhage and lipid-rich plaques. In 2011, a study by Jansen et al. on *ex-vivo* human coronary plaques, demonstrated that lipid component of vulnerable plaques can be identified with an intravascular PA imaging system [32]. To improve the PA detection sensitivity, the group of Cheng developed an intravascular PA imaging system that was based on a collinear alignment of the incident optical wave and the photoacoustically generated sound wave. It was found to allow reliable access of the entire arterial wall, including perivascular fat [33].

PA Imaging of the Skin

The skin and hypodermis are perhaps the most accessible tissues of interest for PA imaging. In 2006, the group of Wang reported a PA microscopy system [34] for melanoma detection. In an immunocompromised nude mouse model, PA microscopy was able to provide 3D high resolution images of both the subcutaneously inoculated melanoma and the surrounding vasculature. In a separate study, PA microscopy was able to clearly visualise a nevus located on the forearm of the volunteer and detailed surround microvasculature [35]. Developed a multimodal PA and optical coherence tomography system that used an all optical detection scheme for imaging of the skin [36]. The system was able to provide three-dimensional *in-vivo* images of the vasculature and the surrounding tissue micro-morphology to a depth of 5 mm in the human skin. This dual-contrast imaging system could be valuable for characterising a range of skin conditions such as tumours, vascular lesions, and soft tissue damage. Most recently, Aguirre developed an ultra-broadband PA mesoscopy system for assessment of dermatological conditions such as psoriatic skin. In which, in a pilot study, good correlation was observed between the calculated index of PA features and the psoriasis area severity index [37].

PA imaging holds tremendous promise to become a valuable tool in many clinical contexts that extend far beyond the applications that were presented above. These applications include but are not limited to imaging of synovial joints for detection of rheumatoid arthritis, ophthalmic imaging, brain imaging, thyroid imaging and prostate imaging [38-42]. With the rapid advancement of PA imaging, new phenomena and technologies are continuously being discovered. More clinical applications and higher impact of this technique on clinical practice are expected in the near future.

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